Restrictive lung disease in β-thalassemia major is associated with myocardial iron overload

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Abstract

Background: Pulmonary dysfunction has been reported in patients with β-thalassaemia major but data are conflicting and the association with iron overload remains unclear. Objectives: To determine the pattern of pulmonary dysfunction in patients with β-thalassaemia major and their associations with iron overload. Methods: Subjects with β-thalassaemia major were recruited for lung function assessment. Serum ferritin and magnetic resonance imaging (MRI) measurements of iron status of the myocardium and the liver were used as surrogate indexes of body iron content. A subgroup of this cohort provided data on the longitudinal progress of their lung function. Results: One hundred and one patients were recruited with a mean age of 25.1 years (SD 7.9 years). Thirty-eight (38%) and five (5%) had restrictive and obstructive lung function deficits, respectively. There was a significant correlation between MRI myocardial T2* relaxation time and forced vital capacity (r=0.291, p=0.048). Higher MRI cardiac T2* relaxation time was associated with lower risk of having restrictive lung function deficit (Odds ratio (OR): 0.94; 95% CI: 0.89-0.99; p=0.023) after adjusting for age, gender and BMI. Twenty-three subjects underwent lung function reassessment with a mean follow-up duration of 13 years. Overall, they did not demonstrate significant changes in pulmonary function over time, 3 patients who had normal lung function at baseline developed restrictive abnormality at follow-up. Conclusions: Restrictive lung disease is prevalent in patients with β-thalassaemia major, and the severity correlates with myocardial iron overload. Monitoring of lung function in this group of patients is important, particularly for those with iron overload.

Title: **Ρεστριςτιε λυνγ δισεασε ιν β-τηαλασσεμια μαθορ ις ασσοςιατεδ ωιτη μψοςαρδιαλ ιρον οερλοαδ**

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ABSTRACT

Background: Pulmonary dysfunction has been reported in patients with β-thalassaemia major but data are conflicting and the association with iron overload remains unclear.

Objectives: To determine the pattern of pulmonary dysfunction in patients with β-thalassaemia major and their associations with iron overload.

Methods: Subjects with β-thalassaemia major were recruited for lung function assessment. Serum ferritin and magnetic resonance imaging (MRI) measurements of iron status of the myocardium and the liver were used as surrogate indexes of body iron content. A subgroup of this cohort provided data on the longitudinal progress of their lung function.

Results: One hundred and one patients were recruited with a mean age of 25.1 years (SD 7.9 years). Thirty-eight (38%) and five (5%) had restrictive and obstructive lung function deficits, respectively. There was a significant correlation between MRI myocardial T2* relaxation time and forced vital capacity (r=0.291, p=0.048). Higher MRI cardiac T2* relaxation time was associated with lower risk of having restrictive lung function deficit (Odds ratio (OR): 0.94; 95% CI: 0.89-0.99; p=0.023) after adjusting for age, gender and BMI. Twenty-three subjects underwent lung function reassessment with a mean follow-up duration of 13 years. Overall, they did not demonstrate significant changes in pulmonary function over time, 3 patients who had normal lung function at baseline developed restrictive abnormality at follow-up.

Conclusions: Restrictive lung disease is prevalent in patients with β-thalassaemia major, and the severity correlates with myocardial iron overload. Monitoring of lung function in this group of patients is important, particularly for those with iron overload.

Keywords: Thalassemia major, pulmonary dysfunction, restrictive lung disease, iron overload, myocardial

Abbreviations:

BMI - body Mass Index

CI - confidence interval

DL_{CO} - diffusing capacity of the lung for carbon monoxide

DLco/VA - diffusing capacity of the lung for carbon monoxide divided by alveolar volume

FEV1 - forced expiratory volume in 1 second

FVC - forced vital capacity

IQR – interquartile range

MRI - Magnetic resonance imaging

SD – standard deviation

TLC - total lung capacity

VA - alveolar volume

INTRODUCTION

βeta-thalassemia major is a genetic disorder characterised by abnormal hemoglobin synthesis, which results in ineffective erythropoiesis, hemolysis, impairment in oxygen delivery to various tissues, and severe transfusion-dependent anemia.(1) While regular blood transfusion is the mainstay of management for patients with β-thalassemia major, iron overload from repeated blood transfusions remains a major cause of multi-organ morbidities in this group of patients despite the availability of iron chelation therapy.(1) The heart, liver, and endocrine glands are the organs known to be most frequently affected.(1) However, effects on the lungs in patients with β-thalassemia major are much less studied and the literature data are contradictory.(2)

Pulmonary dysfunction has been reported in up to 80% of patients with β-thalassemia major.(3,4) The pulmonary abnormalities identified in previous studies include restrictive lung disease (2,5–12), small airway disease (5), obstructive lung deficits (3,10–12), and impaired diffusion capacity for carbon dioxide.(2,8,9,11,12) Although the pathophysiology of pulmonary dysfunction is poorly defined, iron accumulation from repeated blood transfusions has been proposed as the likely cause.(2,3,13–16) This is supported by autopsy data and post-mortem examinations, which found pulmonary iron deposition in thalassemia major patients who had previously received multiple transfusions.(17,18)

Serum ferritin levels provide a measure of the body's iron status and high levels correlate with iron overload in patients with β-thalassemia major.(19) Magnetic resonance imaging (MRI) is increasingly being used to quantify iron deposition in organs such as the heart and the liver.(1) Currently cardiac MRI is a widely adopted non-invasive tool for monitoring iron overload in the heart, which has the advantage of being able to detect myocardial iron overload earlier than echocardiogram identified ventricular dysfunction.(20,21) MR T2-star (T2*) technique can reproducibly quantify myocardial iron deposition that a lower T2* relaxation time represents higher iron overload status. Nonetheless, the relationship between this MRI marker of iron status and pulmonary dysfunction in patients with β-thalassemia major remains to be ascertained. A previous study did not find a correlation between lung function deficits with cardiac or liver iron overload.(2) However, among patients with high serum ferritin, a lower cardiac T2* was observed in patients with restrictive lung disease.(2) Data on the secular trend of lung function in patients with β-thalassemia major is also scarce. A previous study that examined 18 adult β-thalassemia major patients, at baseline and 7 years later could not demonstrate significant differences in lung function parameters between the two time points.(7) The same research group reassessed 30 patients from the initial cohort after a further 10 years and similarly no significant change was documented in any of the lung function parameters.(2) However, the subjects involved were already in their adulthood at baseline. Our group has established a cohort of patients with β-thalassemia major and reported their lung function at a mean age of 14.2 years.(11) Repeat assessment would allow informative observation on the natural progression of their lung function.

In this study, we aimed 1) to identify the patterns of pulmonary function deficits in a cohort of β -thalassemia major patients; 2) to examine the correlations between pulmonary function abnormalities with serum ferritin and MRI measurements of iron content in the myocardium and the liver; 3) to compare pulmonary function test parameters between two time points in a subgroup of patients.

STUDY DESIGN and METHODS

Study Design and Participants

Patients diagnosed with β-thalassemia major and being followed up at the four participating hospitals (Prince of Wales Hospital, Princess Margaret Hospital, Tuen Mun Hospital, and Queen Mary Hospital) were identified. Inclusion criteria were (1) age above 6 years at the time of recruitment, (2) on regular blood transfusions to maintain hemoglobin level at or above 10g/dl, and (3) free from symptoms of respiratory tract illness for at least 2 weeks before lung function assessment. Exclusion criteria were any cardio-pulmonary conditions for example pulmonary hypertension, congestive heart failure, or chronic lung disease that restricted the subject from physical exertion. Written informed consent was obtained from the eligible subjects or their parents if they were younger than 18 years of age. Ethics approval was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Reference number: 2012.128).

Data collection and anthropometric measurements

Past medical history and relevant clinical information with regards to transfusion history were obtained from the case notes. The most recent ferritin levels were retrieved from the medical record. The measurements of the heart and liver T2* relaxation time were retrieved from the computerized clinical management system. Only data within 12 months from the lung function measurement were included in the analysis. The radiologists involved in the MRI reporting were not involved in the study and were blinded to the patients' lung function measurements. Serum ferritin, magnetic resonance imaging (MRI) measurements of the myocardium and liver were used as surrogate indexes of body iron content. The height and weight of each subject were measured for determining the body mass index (BMI). Standing height without shoes was measured using a Harpenden stadiometer (Holtain, UK) to the nearest 0.1 cm. Bodyweight was measured with the lightest clothing to the nearest 0.1 kg by an electronic weighing scale (Tanita BF-522, Japan).

Lung function measurements

All subjects were invited to have lung function measurements before the scheduled transfusion. A lung function test was performed according to the recommended standard.(22,23) Spirometry was measured by a SensorMedics 2130 spirometer using the Enhanced Spirometry Program. The best of at least three technically acceptable values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and flow-volume curves were selected. Total lung capacity (TLC) was measured by body plethysmography (SensorMedics 6200) and expressed in liters corrected for body temperature, atmospheric pressure, and saturation with water vapour. The diffusion capacity of carbon monoxide was measured by single breath technique and the values obtained were corrected for hemoglobin concentration (SensorMedics 6200 Autobox DL, Single Breath Diffusion Capacity DLco SB Program). The pulmonary function results were expressed as percentages of predicted normal values.(24) For this study, the threshold of abnormality was defined as under 80% of the predicted value. A restrictive deficit was defined as a reduction in TLC or FVC to less than 80%; diffusion impairment as a reduction in diffusing capacity divided by the alveolar volume (DL_{CO}/VA) to less than 80%, and obstructive airway disease as reduced FEV_1 and FEV_1/FVC ratio to less than 80%.

Statistical analysis

Patient characteristics were described using frequencies for categorical variables, means and standard deviations (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for skewed data. Pulmonary function test variables were expressed as a percent of predicted value according to local references.(24) T -test, Mann-Whitney U, and chi-square tests (or Fisher's exact if appropriate) were used for normally distributed, skewed, and categorical data, respectively, to assess differences in clinical characteristics between patient groups. Correlations between lung function results, serum ferritin level, and MRI measurements were assessed by Pearson Correlation. Non-parametric variables were log-transformed with normality checked before correlation assessment. Logistic regression was used to assess risk factors associated with pulmonary function deficits. For the subgroup with baseline and follow-up lung function

assessment performed, a paired-samples$t$ -test was used to assess changes in lung function parameters over time. Statistical analyses were performed using SPSS statistical software package V.25.0 for Windows. P values <0.05 were considered significant.

RESULTS

Sample characteristics

One hundred and one patients were recruited (mean age: 25.1 ± SD 7.9 years) and 52 (51%) were males. The median age at the diagnosis of β-thalassemia major was 0.8 years (Interquartile range (IQR): 0.5-2.0 years) and the mean duration of regular blood transfusions was 23.3 ± 8.0 years). The characteristics of the participants are shown in Table 1. No patients had clinical symptoms or signs of lung disease.

Lung function patterns of the subjects

Fifty-two subjects (51%) had a normal lung function. Thirty-eight (38%) and five (5%) subjects had restrictive and obstructive lung function deficits, respectively. One (1%) had impaired diffusion capacity. Five subjects (5%) had mixed lung function deficits: two had mixed restrictive and obstructive patterns, one had mixed restrictive deficit and impaired diffusion capacity, one had mixed obstructive pattern and impaired diffusion capacity, and one had mixed restrictive obstructive patterns and impaired diffusion capacity. As restrictive lung function deficit was the predominant deficit observed, a comparison between subjects with normal lung function and those with restrictive lung deficit is shown in Table 2. As expected, patients with restrictive lung function deficit had significantly lower FVC % predicted (75.5%, IQR: 68.0-82.0% vs 91.0%, IQR: 87.0-94.8%, p<0.001) and TLC % predicted (74.5%, IQR 67.3-78.8% vs 91.0%, IQR 85.0-100.0%, p<0.001) than the individuals with normal lung function. As FEV1 and FVC are closely related, patients with restrictive lung function deficit also had significantly lower FEV1 % predicted (77.0%, IQR: 70.0-83.3% vs 92.0%, IQR: 84.0-98.0%, p<0.001) than those with normal lung function. There were no significant differences in other characteristics such as age, gender, weight, height, BMI, duration of regular blood transfusion, and serum ferritin concentrations.

Fourteen and 29 subjects with restrictive and normal lung function, respectively had cardiac MRI data available within 12 months from the lung function assessment. Former group had significantly lower MRI cardiac T2* relaxation time than those with normal lung function (26.5 ± 13.2ms vs 40.1 ± 18.2ms, p=0.017) (Table 2).

When only taking those with available MRI measurements into consideration, those with restrictive lung function deficit had a male gender predominance (64%) and significantly higher body weight and height when compared to those with normal lung function (Supplementary Table 1). There were no significant differences in other characteristics such as age, gender, BMI, duration of regular blood transfusion, and serum ferritin concentrations between those with normal lung function and those with restrictive lung function deficit.

Correlations between lung function and surrogate indexes of body iron content

There was a significant correlation between myocardial T2*relaxation time on MRI measurement and FVC %Predicted (r=0.291, p=0.048), while a correlation with TLC %Predicted was not observed. (Table 3) A significant correlation was also detected between myocardial T2* relaxation time and FEV1 %Predicted (r=0.324, p=0.026). Serum ferritin level was inversely correlated with DL_{CO}/VA %Predicted (r=-0.235, p=0.021). In logistic regression analysis, higher MRI cardiac T2* relaxation time was associated with a lower risk of having restrictive lung function deficit (Odds ratio (OR): 0.94; 95% CI: 0.89-0.99; p=0.023) after adjusting for age, gender and BMI.

Longitudinal evaluation of a subgroup

This study included 23 subjects (13 males) who underwent lung function assessment 13 years ago. There were no statistically significant differences in the clinical characteristics between subjects who had longitudinal lung function data and those who did not (Supplementary Table 2). Longitudinal changes in lung function over time are shown in Table 4. DL_{CO}/VA was not available at baseline and therefore only comparison in

DL_{CO} was performed. The decrease in the FVC %Predicted just reached borderline statistical significance. Overall, these 23 subjects did not have significant changes in their pulmonary function over time. At baseline, four subjects had restrictive lung function deficit, three of them continued to have restrictive pattern at follow-up. Three patients who had normal lung function at baseline developed restrictive abnormality at follow-up. Further statistical analysis was not performed given the small subject number.

DISCUSSION

Our study demonstrated that restrictive lung function deficit was commonly seen in individuals with β-thalassemia major. There was a significant correlation between myocardial T2 * relaxation time on MRI measurement and FVC %Predicted. Higher MRI cardiac T2* relaxation time was associated with a lower risk of having restrictive lung disease. The findings suggested that myocardial iron overload was associated with restrictive lung function deficit in patients with β-thalassemia major.

Our cohort shared a similar prevalence of restrictive lung function deficits with published studies.(2,7) *Guidotti* et al summarised the literature data on pulmonary function in patients with thalassemia major.(2) The study results have been heterogeneous in terms of the pattern of pulmonary abnormalities observed. However, restrictive lung disease has been commonly reported in many of the studies with a prevalence ranging from 13.8% to 79%.(2) Although the exact pathophysiological mechanism is not known, iron accumulation in the lungs and chronic hypoxia related to chronic anemia are believed to be important factors contributing to the development of pulmonary dysfunction in patients with thalassemia major. It is hypothesized that iron accumulation could cause lung parenchymal fibrosis through the production of potentially toxic hydroxyl radicals, and hence lead to restrictive disease and impaired diffusion capacity.(28) Our study is one of the few that found an association between restrictive lung function deficit and markers of iron overload. Interestingly, such correlation was observed in myocardial T2* relaxation time only but not other markers such as serum ferritin or liver T2*, although the serum ferritin level was inversely correlated with the diffusing capacity. Another study reported a lower cardiac T2* in patients with restrictive lung disease when compared to those without restrictive pattern, yet the difference was observed only in patients with high serum ferritin.(2)*Parakh et al.* evaluated pulmonary function in 31 patients with β-thalassemia major, and in those with abnormal results computed tomography (CT) of the chest and bronchoalveolar lavage (BAL) were also performed.(12) In the 15 patients with pulmonary deficit, bronchial dilatation and air trapping signifying small-airway disease were the commonest findings on chest CT, and iron-laden macrophages were demonstrated in 14 out of the 15 BAL samples. They have also detected a significant inverse correlation between DLco and serum ferritin, which was consistent with our observation. Moreover, a previous study reported improvements in lung function when good control of iron status was achieved with optimal chelation therapy.(7) Overall, the findings supported the hypothesis that iron overload is an important culprit of pulmonary dysfunction in patients with β-thalassemia major. However, it is important to be aware that the associations between pulmonary dysfunction and iron accumulation were not demonstrated in all studies.(29) In fact, some autopsy studies with small sample size did not detect any fibrosis or increase of hemosiderin in the lungs from patients with β-thalassemia major.(30,31) Therefore, more studies would be needed to elucidate the pathogenesis of lung function impairment in this group of patients. As our study demonstrated the association between restrictive lung function deficit and myocardial iron accumulation, future studies should also investigate whether myocardial iron overload and dysfunction would cause pulmonary disease through the complex cardiopulmonary interrelation.

Reduced lung function is an independent factor associated with overall and cardiovascular mortality, the observed pulmonary abnormalities are clinically relevant taking into account the enhanced life expectancy of patients with β-thalassemia major.(25–27) Therefore, regular pulmonary function assessment should be incorporated in the management plan of patients with β-thalassemia major. Early detection of lung function abnormalities, timely pulmonary rehabilitation and avoidance of risk factors such as smoking and exposure to environmental tobacco smoke are important measures to slow down lung function decline. The subgroup in our study demonstrated that three out of 19 patients who had normal lung function at baseline developed restrictive lung function deficit at follow-up. However, the sample number was too small to identify risk

factors of lung function decline. Further studies would be needed to study the predictive factors, long-term outcomes, and implications of the demonstrated pulmonary dysfunction.

There were a few limitations in our study. Our study was not able to address the pathogenesis of pulmonary dysfunction in patients with β-thalassemia major. Although iron overload has been the principal hypothesis, other factors were not evaluated in our study, such as the effect of chronic hypoxia, skeletal changes and abnormal chest conformation on lung growth and ventilation mechanics.(2) Moreover, our study was not able to eliminate the potential confounding effect from iron chelation therapy, while desferrioxamine has been suggested as a potential cause of lung function impairment.(32,33) Patients with iron overload were all on iron chelation therapy and very likely those with more severe iron overload were on a higher dosage of iron chelation. More studies are needed to evaluate how iron chelation therapy impacts lung function. Finally, the sample size and the study power were limited by the number of patients under the care of the study centres. Only some of the patients had available MRI data for analysis which might cause potential bias. Moreover, the sample size of the subgroup who had lung function reassessment was too small to evaluate the natural history of pulmonary disease and to identify risk factors of lung function decline.

CONCLUSION

Restrictive lung disease is prevalent in patients with β-thalassemia major. A significant association between restrictive lung disease and myocardial iron accumulation was observed. As lung function decline is associated with significant morbidity and mortality, it would be important to incorporate regular pulmonary function assessment in the management plan of patients with β-thalassemia major. Future studies should further evaluate the pathogenic mechanism and the long-term outcomes of pulmonary dysfunction in this particular patient group.

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Author contributions:

Kate C Chan: Dr. Chan conceptualized and designed the study, coordinated subject recruitment, supervised and performed data collection, carried out data analysis and interpretation, drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

Chun T Au: Dr. Au designed the study, contributed to subject recruitment and data collection, performed data analysis and interpretation, revised the manuscript, and approved the final manuscript as submitted.

Alex WK Leung: Dr. Leung contributed to study design, coordinated subject recruitment, contributed to data analysis and interpretation, revised the manuscript, and approved the final manuscript as submitted.

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Table 1. Clinical characteristics of the participants (N=101)

Characteristics	Value
Age (years)	25.1 ± 7.9
Male sex, n (%)	52 (51.5%)
Weight (kg), median (IQR)	48.1 (41.8 – 52.9)
Height (cm), median (IQR)	155.5 (149.0 – 161.9)
BMI (kg/m^2)	20.0 ± 2.5
Age at diagnosis (years), median (IQR)	0.8 (0.5 – 2.0)
Age of starting regular blood transfusion (years), median (IQR)	1.0 (0.5 – 3.0)
Duration of blood transfusion (years)	23.3 ± 8.0
Serum ferritin (pmol/L), median (IQR)	4118.0 (2505.5 – 6459.5)
MRI cardiac T2* relaxation time (ms) (N=47)	34.7±17.9
MRI liver T2* relaxation time (ms), median (IQR) (N=36)	4.7 (2.3 – 10.9)

Values are presented as mean ± standard deviation unless otherwise specified.

BMI: body mass index; IQR: interquartile range; MRI: magnetic resonance imaging

Table 2. Comparisons of clinical characteristics between participants with normal lung function and those with restrictive lung disease

Characteristics	Normal (n = 52)	Restrictive (n = 38)	*P*
Age (years), mean ± SD	24.9 ± 7.8	25.6 ± 8.1	0.706
Sex, n (%)	F: 24 (46.2%) M: 28 (53.8%)	F: 20 (52.6%) M: 18 (47.4%)	0.670
Weight (kg)	45.6 (41.4-50.8)	49.3 (42.9-53.5)	0.140

Characteristics	Normal (n = 52)	Restrictive (n = 38)	*P*
Height (cm)	153.4 (148.3-159.8)	156.5 (150.0-161.9)	0.261
BMI (kg/m^2), mean ± SD	19.7 ± 2.4	20.4 ± 2.5	0.149
Age at diagnosis (years)	0.8 (0.5-1.5)	0.7 (0.3-2.5)	0.977
Age of starting blood transfusion (years)	1.0 (0.5-3.0)	1.0 (0.5-3.0)	0.629
Duration of blood transfusion (years), mean ± SD	23.4 ± 7.8	23.5 ± 8.3	0.939
Serum ferritin (pmol/L)	3625.0 (2381.5-5983.0)	4474.0 (2349.8-6054.8)	0.551
FVC (% predicted), mean ± SD	91.9 ± 7.9	74.2 ± 9.3	<0.001
FEV1 (% predicted), mean ± SD	92.0 ± 9.0	76.6 ± 9.1	<0.001
FEV1/FVC (%)	88.0 (85.0-91.8)	91.0 (89.0-93.3)	0.005
FEV1/FVC (% predicted)	100.5 (96.0-104.0)	103.0 (101.0-108.0)	0.001
TLC (% predicted)	91.0 (85.0-100.0)	74.5 (67.3-78.8)	<0.001
DLCO/VA (% predicted)	112.0 (101.0 – 130.5)	129.0 (113.3-141.3)	0.010
MRI cardiac T2* relaxation time (ms), mean ± SD	40.1 ± 18.2 (N= 29)	26.5 ± 13.2 (N= 14)	0.017
MRI liver T2* relaxation time (ms), median (IQR)	5.1 (2.2-10.9) (N= 24)	3.8 (2.4-12.0) (N= 9)	0.766

Values are presented as medial and interquartile range (IQR) unless otherwise specified.

P values by t-test, Mann-Whitney U and chi-square test for parametric, non-parametric, and categorical variables respectively

BMI: body mass index; SD: standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; MRI: magnetic resonance imaging

Table 3. Correlations between lung function and surrogate indexes of body iron content

Measurements	FVC (% Pred)	FEV1 (% Pred)	FEV1/FVC (%) (log-transformed)	TLC (% Pred) (log-transformed)	DLCO/VA (% Pred) (log-transformed)
Serum ferritin (log-transformed)	r = 0.015 p = 0.884	r = -0.027 p = 0.786	r = -0.091 p = 0.367	r = -0.108 p = 0.297	r = -0.235 p = **0.021**
MRI cardiac T2* relaxation time	r = 0.291 p = **0.048**	r = 0.324 p = **0.026**	r = 0.088 p = 0.557	r = 0.267 p = 0.077	r = -0.036 p = 0.812

Measurements	FVC (% Pred)	FEV1 (% Pred)	FEV1/FVC (%) (log-transformed)	TLC (% Pred) (log-transformed)	DLCO/VA (% Pred) (log-transformed)
MRI liver T2* relaxation time (log-transformed)	r = 0.074 p = 0.670	r = 0.052 p = 0.762	r = -0.070 p = 0.684	r = 0.154 p = 0.369	r = 0.031 p = 0.860

Correlations were performed by Pearson Correlation

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; MRI: magnetic resonance imaging

Table 4. Longitudinal changes in lung function over time (N=23)

Characteristics	Baseline	Follow-up	*P*
Age	13.73 ± 3.80	26.79 ± 3.62	-
FVC (% predicted)	90.83 ± 12.22	86.13 ± 11.85	0.050
FEV1 (% predicted)	86.57 ± 11.59	85.48 ± 11.52	0.566
FEV1/FVC (%)	86.91 ± 4.99	87.70 ± 3.43	0.364
TLC (% predicted)	96.10 ± 16.82	88.50 ± 19.11	0.092
Log-transformed TLC	4.55 ± 0.19	4.46 ± 0.20	0.059
DL_{CO} (% predicted)	90.86 ± 22.73	93.27 ± 30.03	0.660
Log-transformed DL_{CO}	4.48 ± 0.24	4.49 ± 0.07	0.926

Values are presented as mean ± standard deviation unless otherwise specified.

P values by paired sample t -test

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; DL_{CO}: diffusing capacity of the lung for carbon monoxide

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